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The Children Leukemia Group: 30 years of research and achievements

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Abstract

The EORTC Children Leukemia Group (CLG) is part of the offspring of the EORTC Hemopathies Working Party which in 1978 split into a paediatric and to an 'adult' branch. At that time, the Berlin-Frankfurt-Munster (BFM) designed by H. Riehm for acute lymphoblastic leukaemia (ALL) appeared much more efficacious than all others and the CLG decided to adapt that treatment strategy for its own clinical trials. The main results of these may be summarised as follows:

- for standard risk patients, the deletion of cyclophosphamide from consolidation and reconsolidation courses does not jeopardise the patient's outcome
- for medium- and high-risk patients receiving high-dose methotrexate (MTX), cranial radiotherapy is superfluous
- with the dose scheduling of the BFM regimen, *E-Coli* L-Asparaginase is more efficacious than *Erwinia* L-Asparaginase
- the addition of monthly intravenous (i.v.) 6-mercaptopurine to conventional maintenance chemotherapy is detrimental
- the assessment by quantitative polymerase chain reaction (PCR) of minimal residual disease at completion of induction is feasible in a cooperative setting and can be used as a powerful and independent prognostic factor.

The CLG also conducted clinical studies of acute myeloblastic leukaemia. Since 1989, lymphoblastic non-Hodgkin's lymphomas have been treated within the ALL trials. The CLG collaborates with other Groups within the I-BFM Study Group and participants in the meta-analytic studies conducted by the Oxford team by the Oxford Children ALL Collaborative Group.

Keywords: EORTC; Children; Leukaemia; Lymphoma; Review

1. Acute lymphoblastic leukaemia studies

1.1. EORTC 58741 trial

The very first EORTC trial (58741) for acute lymphoblastic leukaemia (ALL) in children and adults was carried out by the EORTC Hemopathies Working Party and coordinated by Dr Pierre Stryckmans. Between 1971 and 1978, patients from Belgian and French centres were registered in this trial, but the great majority of the paediatric patients were from Belgian centres. The patients were randomised to answer two consecutive questions:

- first, at the completion of the induction therapy, the patients who had achieved complete remission, were randomised to receive either three drugs (methotrexate (MTX), vincristine, prednisone) or seven drugs (the same + L-Asparaginase, 6-mercaptopurine, cyclosphophamide,

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BCNU) as consolidation therapy until one year from the start of induction.

- as to the second question, at completion of the consolidation therapy, two types of continuation treatment were compared: either conventional maintenance chemotherapy (6-mercaptopurine + methotrexate and vincristine + prednisolone pulses) or immunotherapy according to Mathé and colleagues (BCG by scarification and intradermal injections of allogeneic non-irradiated leukaemic blast cells).

No difference in disease-free survival or in survival was found between the two consolidation arms. With regard to the second question, disease-free interval was significantly better in the chemotherapy arm, but eventually survival was similar because a high salvage rate was achieved after relapse in the immunotherapy arm [1].

At completion of this trial in 1978, the Hemopathies Working Party, which was to become the Leukemia Cooperative Group, ran further ALL trials in adults. However, by that time, it had become clear that ALL was a heterogeneous grouping of distinct entities, the distribution of which differed in adults and children. As the overall therapeutic results were already much better in children, and as some age-related factors had to be taken into account to optimise the treatment, such as better tolerance to the acute side-effects of chemotherapy in children but, by contrast, their specific sensitivity to some late side-effects of radiotherapy and chemotherapy, it became difficult to design similar treatment protocols and to ask identical questions in both adult and paediatric patients. However, as the paediatric branch of the Hemopathies Working Party was too small to run randomised trials, it had to wait until 1981, when 10 French centres joined the Group to regain the capability to start cooperative studies and trials. Later, four other French centres and two Portuguese centres joined the Group (Table 1).

By the end of the 1970s, the results of the Berlin-Frankfurt-Munster (BFM) ALL protocol, designed by H. Riehm, became known and appeared to be much better than all the others published so far. That protocol differed from most of the others due to its much higher time-dosing intensity throughout the first 6 months of the treatment, which required an optimal and very stringent supportive care in order to avoid an unacceptable toxic death rate. To the majority of paediatric oncologists and haematologists, the BFM ALL protocol seemed hardly feasible. However, the event-free survival (EFS) of children treated with the 1976 BFM protocol in Germany was 70% compared with 40% for the cohort of patients treated in the EORTC 58741 protocol. Therefore, our Group, rebaptised as the EORTC Children's Leukemia Cooperative Group (CLCG), started the 1976 version of the BFM protocol. A total of 141 patients (aged less than 16 years) were registered in this study between January 1981 and July 1983. The stratification of patients in respective standard, medium- and high-risk subgroups was according to the risk factor (RF) as defined by Langermann and as used in the BFM 1976 ALL study [2]. Eventually, in spite of a high toxic death rate during the first year of this pilot study, a 5-year EFS of 70% was achieved [3,4].

1.2. EORTC 58831 and 58832 ALL trials

Encouraged by the favourable results of the pilot study, but still concerned by the possible acute and late toxicities of the BFM protocol, the CLCG participants evaluated two alleviated versions of it. These two studies recruited 735 patients between 1983 and 1988. Again, patients were stratified according to the RF of Langermann: standard risk patients were those with a RF <1.2, medium risk patients those with a RF comprised between 1.2 and 1.69, and high risk patients those with a RF $\geqslant 1.7$. Because cyclophosphamide, which was part of the BFM treatment regimen, was not known to be an important component of the ALL protocols, patients with standard-risk characteristics were randomised to receive or not to receive cyclophosphamide during consolidation and reconsolidation. For medium- and high-risk patients, high-dose methotrexate (four times 5 g/m^2) was added to the BFM regimen between induction–consolidation and reinduction and the subsequent administrations of radiotherapy to the cranium was randomised. By that time, the late deleterious effects of cranial radiotherapy in children with ALL had become evident and were of great concern to paediatricians. For standard-risk patients, who represented 60% of the overall population, no cranial radiotherapy was programmed in the front-line therapy, but they all received four courses of intermediate dose MTX (0.5 g/m^2). Overall, less than 20% of the patients were to receive cranial radiotherapy. At 6 years, the EFS rate ($\pm$standard error (S.E.)) for the whole population was 66% $\pm$ 1.8%, the central nervous system (CNS) relapse (isolated or combined) rate was 11% $\pm$ 1.2% and the survival rate was 79% (Fig. 1) [5]. The deletion of cyclophosphamide did not jeopardise the efficacy of the BFM protocol in standard-risk patients. Likewise, for medium- and high-risk patients, receiving high-dose (HD) MTX, the omission of cranial radiotherapy failed to increase the risk of CNS relapse or of any relapse. This observation led to the deletion of cranial radiotherapy from front-line therapy protocols in subsequent CLCG trials. With regards to cyclophosphamide, at the time the next trial was designed, the definitive results were not available, therefore it was considered premature to delete cyclophosphamide from the treatment protocol of standard-risk patients.

1.3. EORTC 58881 ALL trial

In this trial, which started in October 1989, the treatment regimen remained very similar to that of the previous trial. The main modifications were as follows:

- no cranial radiotherapy was called for, even in patients with initial colony stimulating factor (CSF) involvement (the latter received more intrathecal (i.t). MTX injections and more courses of HD MTX intravenously (i.v.).
- the dose of HD MTX was augmented to 5 g/m^2 for all patients.
- all patients, including those with low-risk characteristics, received the same reinduction–consolidation course previously given to medium- and high-risk patients only.
- a new prognostic factor, the importance of which has been demonstrated by the BFM group, i.e. the number of blasts in the blood after 7 days of a treatment course consisting of prednisone and one i.t. injection of MTX was used to identify a subgroup of patients with very high-risk characteristics.
- patients with lymphoblastic non-Hodgkin's lymphoma were eligible for this study.

In trial 58881, three randomised questions were asked:

1. was there a difference in toxicity and efficacy between the two L-Asparaginase, i.e. *E-Coli* and *Erwinia* L-Asparaginase?
2. For patients with intermediate-risk characteristics, did the addition of high-dose Ara-C to HD MTX, supposedly entailing a synergistic effect, lead to a reduced rate of CNS relapses and a prolonged DFS?
3. For all patients, would the addition of monthly i.v. 6-mercaptopurine (1 g/m^2) to conventional maintenance treatment improve the DFS and survival?

In addition to those therapeutic questions, the issue was addressed of whether it would be possible, within a cooperative setting, to evaluate minimal residual disease by polymerase chain reaction (PCR) amplification of clonal T-cell receptor or immunoglobulin gene rearrangements at different time-points of the treatment and to assess the clinical significance of this measurement. The latter study was done in 11 out of the 24 centres participating in the clinical trial and was carried out between 1993 and 1996.

Overall, 2216 patients were treated according to this protocol, 700 of whom were randomised for the Asparaginase question, 653 were randomised for the Ara-C question and 874 were randomised for the 6-MP i.v. maintenance question. The overall EFS rate was 68.4% ± 1.2% at 8 years and the survival rate was 79% ± 1% at 8 years (Fig. 1). The results of the three

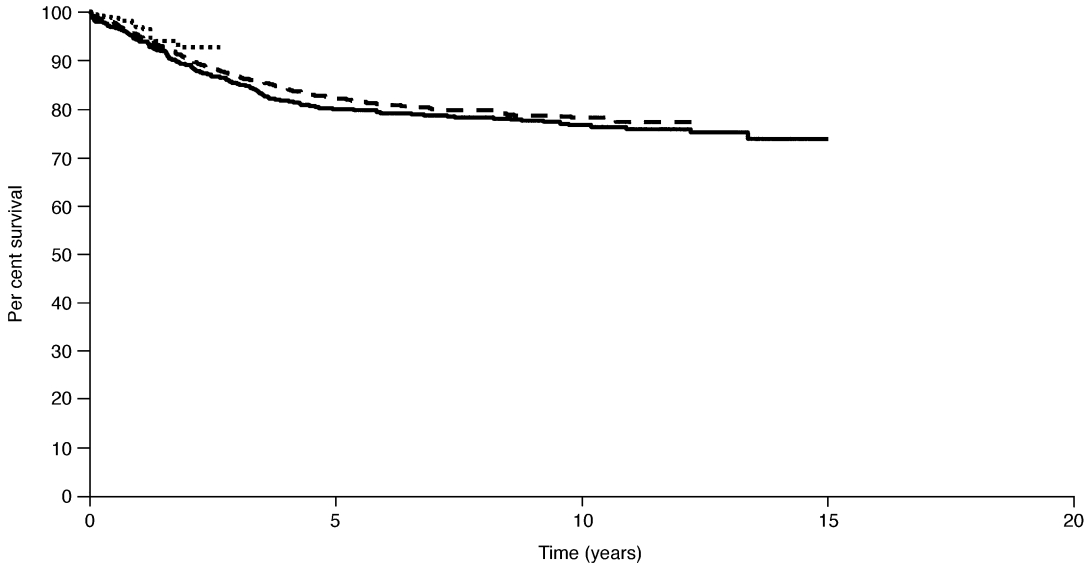

Fig. 1. Duration of survival in three consecutive studies of the CLG in ALL/NHL patients. ALL, acute lymphoblastic leukaemia; NHL, non-Hodgkin's lymphoma; O, observed; N, number.

randomised trials within that study may be summarised as follows:

1. *E-Coli* L-Asparaginase induces more coagulation abnormalities, but does not increase the incidence of clinically significant thrombotic or haemorrhagic complications. *E-Coli* L-Asparaginase is also more efficient than *Erwinia* L-Asparaginase, as evaluated by a lower rate of induction failures (2.0% versus 4.9%), and a higher EFS rate at 6 years (73.4% ± 2.4% versus 59.8% ± 2.6%) [6].
2. These results are in agreement with the presently known pharmacodynamic differences between the two drugs.
3. The addition of high-dose Ara-C to high dose MTX fails to improve the DFS or the CNS-relapse free interval of patients with intermediate-risk characteristics [7].
4. Unexpectedly, the addition of i.v. 6-mercaptopurine to conventional continuation therapy was detrimental, as the DFS rate at 5 years was lower in the arm randomised to receive i.v. 6-mercaptopurine (71.2% ± 2.3% versus 78.6% ± 2.1%) [8].
5. The assessment of minimal residual disease (MRD), which was done in two laboratories working in close collaboration (Paris and Brussels), appeared feasible. The detection and the level of MRD were found to be highly predictive of early relapses [9]. A level of more than 10^{-2} leukaemic cells:mononuclear cells in the bone marrow at completion of induction permitted the identification of a subgroup of patients with a very high risk of early relapse. This prognostic factor was, moreover, shown to be independent of the other most important prognostic factors such as immunophenotype, leucocyte count, age and number of peripheral leukaemic cells at day 8 of the treatment. Evaluation of MRD at completion of induction is currently being evaluated in the ongoing 58951 trial in which a level of MRD $> 10^{-2}$ directs the patients to a very high-risk treatment protocol.

1.4. EORTC 58951 ALL trial

This ongoing trial for ALL and lymphoblastic non-Hodgkin's lymphomas started in December 1998 and has recruited 634 patients so far from seven Belgian centres, 15 French centres and two Portuguese centres.

Three questions are addressed:

1. The relative toxicity and efficacy of dexamethasone (6 mg/m^2/day) and of prednisolone (60 mg/m^2/day) given during induction and, for some patients, during maintenance therapy.
2. Because the results of the 58881 trial suggested that L-Asparaginase was a very important component of the BFM treatment regimen, to evaluate whether the EFS and the survival can be improved by giving L-Asparaginase throughout twice as long a duration as in conventional BFM protocol during induction–consolidation and reinduction. This longer duration of the L-Asparaginase courses entails a doubling of the number of administrations.
3. With regard to the third question, the EORTC Children Leukemia Group has joined an intergroup trial run by the International BFM Study Group in which the addition of glucocorticoid + vincristine pulses during continuation therapy is evaluated in average risk patients.

One foresees that a total of 1500 patients will be recruited in this study.

1.5. Other CLCG clinical studies

1.5.1. Importance of the timing of the first i.t. injection of MTX at the start of induction

In the 58881 trial, all patients with ALL received a pre-induction course combining prednisone during 1 week and one injection of MTX on day 8. About 10% of the patients were expected to have $\geqslant$1000 leukaemic cells/mm^3 at completion of the 7-day course. These patients, considered as poor risk, were committed to the very high-risk treatment. Actually, more than 20% of the first 126 patients eventually fell in this category. When the first i.t. MTX injection was shifted backwards to day 1 of the pre-induction course, the percentage of poor responders decreased to 11.5%, in agreement with previous results reported by the German BFM Group. This serendipitous observation pinpointed the importance of the systemic effect of the i.t. MTX [10].

1.5.2. Results of CLCG treatment protocols in infants with ALL

Age less than 1 year has been shown to be a very bad prognostic factor in ALL. Ferster and colleagues, on behalf of the CLCG, reported results which were achieved in a cohort of infants registered in the 58831 and 58832 trials, and which compared favourably with most others published at that time [11]. Similar results have been obtained in the next cohort of infants treated in the 58881 trial [12]. The factors, which were associated with a bad prognosis, were the presence t(4;11), of CD10 negativity and high white blood cells (WBC). Presently, most CLCG centres register the infants with ALL in the European Interfant Study.

1.6. Acute myeloblastic leukaemia (AML) studies

Due to the much smaller number of paediatric patients with AML, the contribution of CLCG to possible improvements in the treatment of this malignancy has been much more limited than for ALL or non-Hodgkin's lymphoma.

However, the group has conducted one pilot study testing the feasibility and the efficacy of a protocol derived from the German BFM ANLL 1983 regimen. The main difference with the latter regimen was the substitution of mitoxantrone for conventional anthracyclines. The rationale for this change was the hopefully lesser cardiotoxicity of mitoxantrone. A total of 108 patients were recruited in this study between January 1988 and December 1991. The response rate after induction–consolidation was 79%, EFS and survival at 3 years were 41 and 56%, respectively. Patients have been closely monitored by echography and no sign of cardiotoxicity has so far been detected. These results compared favourably with other reported data [13].

Since 1992, a randomised trial (EORTC 57921) addressed the question of the relative efficacy of mitoxantrone versus idarubicin. The treatment regimen was further adapted through the introduction of high-dose Ara-C during a first consolidation course followed by DCTER combination. A total of 215 patients have been recruited so far and the trial might be closed in the near future. The overall EFS and overall survival seem to be superior to the previous study, and compare favourably with recent results reported by other groups. Even if the results of this trial might be inconclusive due to a possible lack of statistical power, they will contribute to a meta-analysis of the same randomised comparison. Indeed, other groups, such as the EORTC Leukemia Group and the Italian GIMEMA, have addressed a similar question in adult AML patients. In future, CLCG will foster the collaboration with other paediatric groups in Europe in order to answer therapeutic questions in a limited period of time.

2. Collaborations with other cooperative groups

In Europe, most cooperative groups for the treatment of acute leukaemia in children are organised on a national or linguistic basis. The EORTC Children's Leukemia Group, albeit presently to French, Belgian and Portuguese centres, is open to paediatric haematology-oncology centres or Groups from all countries. It

Table 1
Members who have participated to CLG studies

Belgium			
	Gent	Universitair Kinderziekenhuis	Drs Y. Benoit/G. Laureys
	Montegnée	Clinique de l'Espérance	Drs N. Francotte/P. Philippet
	Antwerp	Koningin Paola Kinderziekenhuis	Drs P. Maes/E.Michiels/J. Gijselink
	Verviers	Centre Hosp. Pelzer—La Tourelle	Dr M-F. Dresse
	Brussels	Academisch Ziekenhuis (VUB)	Dr J. Otten
	Liège	CHR de la Citadelle	Dr C. Hoyoux
	Leuven	U.Z. Gasthuisberg	Dr A. Uyttebroeck/P. Brock
	Brussels	Hôpital des Enfants	Dr A. Ferster
France			
	Besançon	CHR de Besançon	Dr E. Plouvier
	Grenoble	CHR de Grenoble—La Tronche	Dr D. Plantaz
	Nice	Centre Antoine Lacassagne	Dr A. Thyss
	Lyon	Hôpital Debrousse	Drs N. Philippe/Y.Bertrand
	Strasbourg	Hôpital Universitaire Hautepierre	Drs P. Lutz/A. Babin-Boilletot
	Montpellier	Hôpital Arnaud de Villeneuve	Dr G. Margueritte
	Lille	CHR de Lille	Drs F. Mazingue/B. Nelken
	Paris	Fondation Curie[a]	Dr J-M Michon
	Reims	Hôpital Américain	Drs C. Béhar/M. Muntzer
	Caen	CHRU de Caen	Dr P. Boutard
	Marseille	CHU Timore[a]	Dr G. Michel
	Poitiers	Hôpital Jean Bernard	Dr F. Millot
	Angers	CHU d'Angers[a]	Dr X. Rialland
	Nantes	CHR- Hôtel—Dieu[a]	Dr F. Mechinaud
	Paris	Hôpital Robert Debré	Dr E. Vilmer
	Lille	Hôpital St. Antoine[a]	Dr J-L Demory
	Toulouse	Hôpital des Enfants	Dr A. Robert
Portugal			
	Porto	Hospital I. P. O. Gentil	Dr S. Borges
	Porto	Hospital Escolar San Joao	Dr L. Norton

[a] No longer active.

also favours increased collaborations with other groups and is an active branch of the International BFM Study Group. CLG has contributed to the overviews performed in the framework of the Children ALL Collaborative Group by the Oxford team, on the value of cranial radiotherapy, additional treatment during induction–consolidation, and additional treatment in maintenance.

AML is a rare disease in children. By contrast, ALL is much more frequent, but it covers a grouping of lymphoid malignancies which differ in biological, genetic and clinical characteristics. In future, some of these ALL subtypes may call for specific treatment approaches. For these reasons, further progress in the study and therapy of these malignancies will probably require improved and closer collaboration with other groups, which CLG is very keen to foster. The CLG also endeavours to develop a closer collaboration with laboratory researchers in order to make translational research a clinical reality.

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The late Pierre Stryckmans not only created the Hemopathies Working Party of the EORTC in 1971, but he also helped us in organising the paediatric leukaemia group 10 years later. He took an active part in the design of the first CLG trials and always remained available for advice and encouragement. The Group is greatly indebted to him. In the late 1970s, Hansjorg Riehm spent a lot of time explaining to us how best to implement the BFM treatment regimen which, at that time, seemed hardly feasible. He made us bold enough to offer our patients the benefits of the breakthrough he introduced in the treatment of ALL. The achievements of the CLG would not have been possible without the involvement and contribution of our data managers, Gabriel Solbu and Christine Waterkeyn, and of the laboratory researchers who are in charge of the cytology, cytogenetics, immunology and molecular biological studies: Anne-Marie Manel, Nicole Dastugue, Frank Speleman, Annie Falkenrodt, Martine Fournier, Claude Preudhomme and Hélène Cavé.

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